International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 10, Issue 10, 2018

Original Article

DOCKING STUDY OF ALLICIN WITH SULFONYLUREA RECEPTOR 1, COMPLEX 1 AND PPARγ RECEPTOR ON INSULIN RESISTANCE

MUHAMMAD ANDRE REYNALDI*, HAFRIZAL RIZA, SRI LULIANA

Department of Pharmaceutics, Tanjungpura University, Pontianak, Indonesia
Email: hafrizal.riza@pharm.untan.ac.id

Received: 25 Jun 2018 Revised and Accepted: 17 Sep 2018

ABSTRACT

Objective: Allicin is a potential type 2 antidiabetic. Sulfonylurea receptor 1 (SUR1), nikotinamida adina dinukleotida dehydrogenase (Complex 1) and peroxisome proliferator-activated receptors gamma (PPARγ) are known as important receptors responsible in insulin resistance This study aimed to determine the physicochemical properties, and the affinity of allicin on SUR1, Complex 1 and PPARγ receptors based on the binding energy and the type of interaction.

Methods: The physicochemical properties of allicin were analyzed using ChemOffice, and the binding energy and type of interaction were analyzed using the docking method with Autodock Vina.

Results: The results from the analysis showed allicin has log p (logarithmic partition) 1.35, massa relativity (mr) 162.26 g/mol, and the binding energy of allicin on SUR1, Complex 1 and PPARγ are respectively-4.0;-3.0; and-4.1 kcal/mol. The type of interaction between allicin and receptors is van der waals.

Conclusion: Allicin has good permeability and has the potential to bind to SUR1, Complex 1 and PPARγ receptors contributing to the activity of allicin as antidiabetic.

Keywords; Allicin, SUR1, Complex 1, PPARγ, Autodock Vina

DOI: http://dx.doi.org/10.22159/ijpps.2018v10i10.28105

INTRODUCTION

Diabetes mellitus type 2 is a disease which is shown by a high blood glucose level (hyperglycemia) [1]. World health organization (WHO) reported that the death-rate trend caused diabetic tend to rise four times from 1980 to 2014. It has caused mortality and disability earlier in human life [2]. Same with WHO report, the disease-rate in Indonesia rises two times from 2007 to 2013. In fact, 90% of the morbidity rate is contributed by type-2 diabetes that is started and caused by lifestyle while the rest are contributed by type-1 diabetes that is caused by genetic [3]. Current medication used to treat the disease is limited by the considerable side effect [4]. Therefore, there is a necessary to find alternative medicine. Natural has potential agents for drug development, such as garlic [5].

Previous research has proven that allicin found in garlic extract can lower blood glucose level and improve insulin secretion in type 2-diabetic rats [5]. The mechanism of its action is predicted similarly to sulfonylurea drug due to sulfur and hydrogen atom in allicin. Moreover, allicin has a functional group, thiosulfonate, allowing interaction with the receptor-like sulfonylurea drug [1]. However, its mechanism and drug target site is still unclear. The target and mechanism of drug-receptor are an important field in drug development through chemical-structure modification in order to optimize drug effect [6].

Docking molecule is a computational research method used to analyze potential mechanism action of a drug agent to receptor based on the binding energy and type of interaction contributing to the affinity between drug and receptor. This method is a preliminary study that could show information about potential drug target that could be used to continue to *in vitro* or molecular research such as modification of drug chemical structure [7-9]. In this research, allicin was docked to three receptors, sulfonylurea receptor 1 (SUR1) that is responsible to increase insulin secretion, nikotinamida adina dinukleotida dehydrogenase (Complex 1) activating adenosine monophosphate-activated protein kinase (AMP-K) that is responsible to increase oxidation of free fatty acids, the inhibitor glucose transporter type-4 (GLUT-4) and peroxisome proliferator-activated receptor-gamma (PPARγ) that is responsible for transcription coding of substance activating AMP-K [10-12]. The affinity of drug-receptor was analyzed based on binding energy and type of interaction.

MATERIALS AND METHODS

Preparation of ligand

Three-dimensional (3D) chemical structure of ligand, allicin, in minimal energy was obtained using a computer program ChemDraw 15.0. The structure was stored in pdb format [13, 14].

Analysis of physicochemical properties

Physicochemical properties of allicin such as molecular weight and log p were analyzed using ChemDraw 15.0 [13].

Preparation of receptors

The 3D chemical structure of target receptor, SUR1 (pdb Id.2ff7) and PPARγ (pdb Id.3k8s) were obtained by downloading from data bank RCSB protein. Complex 1 receptor was downloaded from the national center for biotechnology information (NCBI) database and obtained by homology modeling of Swiss software model [15-17].

Molecular docking

Detection of receptor active sites, docking, and analysis of amino acids of receptors bound to ligand were conducted using Autodock Vina (Version 1.1.2) with the help of Autodock tools (ADT) and discovery studio to analyze ligand-receptor binding interaction [7, 14].

Data analysis

The analysis result of ligand physicochemical properties (log p, mr, H acceptor, and donor) was using ChemDraw 15.0 and interpreted based on the rule of five Lipinski to predict ligand absorption and permeability properties. Determination of amino acids involved in the interaction between receptor and drug, and the binding energy (kcal/mol) was obtained using Autodock Vina (version 1.1.2) [8, 9, 18].

RESULTS AND DISCUSSION

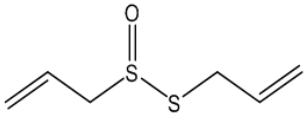

Fig. 1: Allicin 2D structure obtained using ChemDraw 15.0

The analysis result of ligand physicochemical properties (table 2) showed that allicin has a molecular weight that is less than 500, log p is less than 5, the number of H donors (group OH and NH) is 0, and the number of H acceptors (atomic O and N) is 1, and log p is less than 5. According to the rule of Five Lipinski, the number of H donors that has good permeability is less than 5, the number of H acceptors that has good permeability is less than 10 and the molecular weight of substance that can penetrate biological membranes is less than 500 g/mol and Log P (solubility in octanol/water) value that describes the ability of a compound to dissolve in liquid of biological membrane is less than 5. Based on the data above, it can be concluded that allicin meets the requirements rule of Five Lipinski, means that allicin can be absorbed and distributed in the body [19].

Table 1: Results determination of chemical compounds physical properties ligands

Molecule name	Log P	Weight Moleculer (g/mol)
Allicin	1.35	162.26
Glibenclamide	3.53	494.004
Metformin	0.15	129.164
Pioglitazon	3.58	356.44

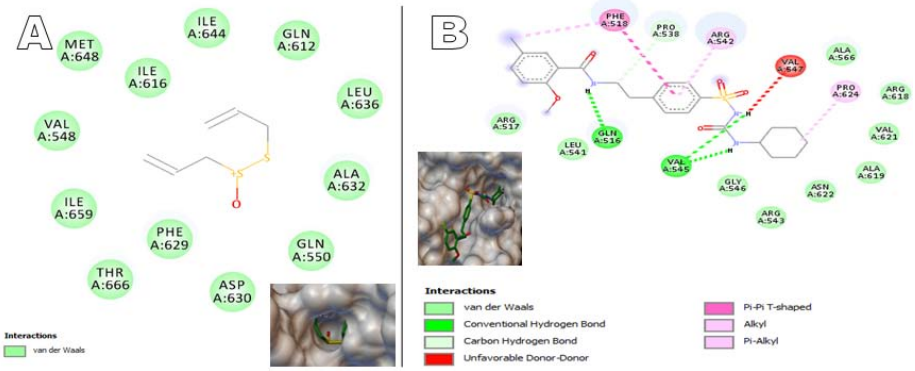

Fig. 2: Molecular docking interaction with ligand amino acid residues; A) Interaction residue SUR1-Allicin, B) Interaction residue SUR1-glibenclamide

Table 2: Binding energy of ligand bond SUR1 obtained Autodock Vina 1.1.2

Molecules names	Binding energy score (kcal/mol)	RMSD
Allicin	-4.0	0.000
Glibenclamide	-8.6	0.000

Docking result shows that the affinity of allicin to the receptor is lower than positive control, glibenclamide affinity for receptor as shown in table 2. This lower affinity of allicin can be caused by the amount of amino acid residue in the active site of receptor bound to allicin that are less than amino acid residue in the active site of receptor bound to glibenclamide. In spite of that, the binding site of allicin is at the active site of receptor bound to positive control showed in fig. 2, so these can contribute the activity of allicin as potential antidiabetic, but it is not as high as a positive control [7, 20].

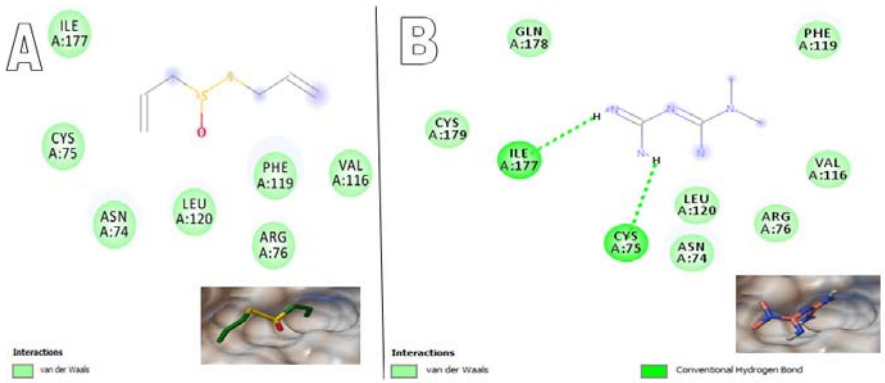

Fig. 3: Molecular docking interaction with ligand amino acid residues; A) Interaction residue complex 1-Allicin, B) Interaction residue complex 1-metformin

Table 3: Binding energy of ligand bond complex 1 obtained autodock vina 1.1.2

Molecules names	Binding energy score (kcal/mol)	RMSD
Allicin	-3.0	0.000
Metformim	-3.6	0.000

Docking result of the allicin affinity to Complex 1 receptor is close to positive control binding energy, metformin to the receptor. It can be caused by the amount of amino acid residue in the active site of receptor bound to allicin and type of interaction involved that is close to metformin, showed in fig. 3. Therefore, these can contribute to the activity of allicin as potential antidiabetic [7, 20].

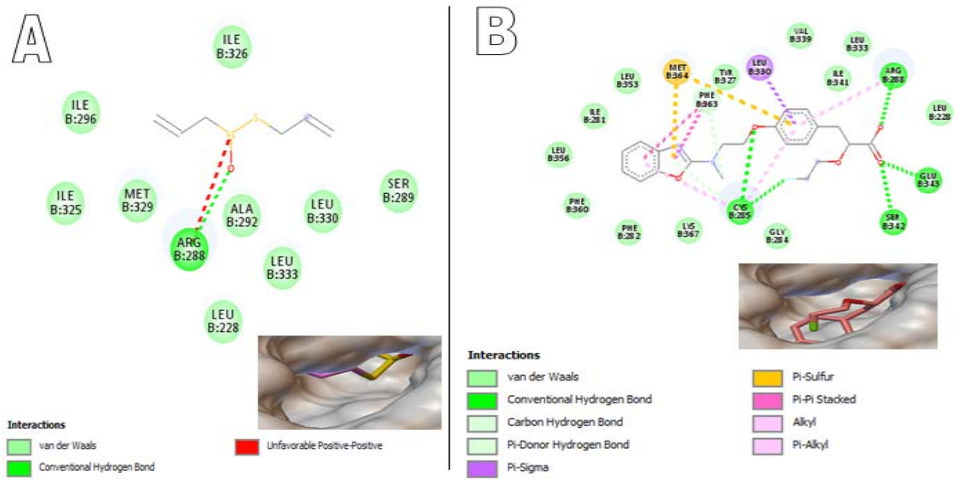

Fig. 4: Molecular docking interaction with ligand amino acid residues; A) Interaction residue PPARγ-Allicin, B) Interaction residue PPARγ–pioglitazon

Table 4: Binding energy of ligand bond PPARγ obtained autodock vina 1.1.2

Molecules names	Binding energy score (kcal/mol)	RMSD
Allicin	-4.1	0.000
Pioglitazon	-8.2	0.000

Docking result shows that the affinity of allicin to the receptor is lower than positive control, pioglitazone affinity to PPARγ as shown in table 4. This lower affinity of allicin can be caused by the amount of amino acid residues in the active site that are less than amino acid residue in the active site of receptor bound to pioglitazone. In spite of that, the binding site of receptor bound to allicin is at the active site of receptor bound to positive control showed fig. 4, so these can contribute the activity of allicin as potential antidiabetic, but it is not as high as a positive control [7, 20].

The active site of the receptor used to bind to allicin is set same with the positive control active site. It is conducted by setting the same dimension for both ligands. The analytical method of allicin binding energy bound to SUR1, Complex 1 and PPARγ receptors had also been validated by RMSD score. The score shows that there is no significance difference between replicated analysis from many conformations. In other studies showed that there is a relationship between docking studies and *in vitro* studies of the isolated pyran ester from Tragia cannabina and Ocimum sanctum which can reduce significant glucose levels [21, 22]. Although the binding score and RMSD showed that allicin is able to bind to the receptor, it was based on the calculation of the theoretical approach [23]. We need to conduct a research experiment to obtain the information about the allicin activity as antidiabetic, especially related to the quantity of compound that has antidiabetes activity.

CONCLUSION

Based on the analysis of physicochemical properties show that allicin has good permeability, and the docking result show that allicin has the potential to bind to SUR1, Complex 1 and PPARγ receptors contributing to the activity of allicin as antidiabetic.

ACKNOWLEDGMENT

The author expresses thankful the Medical Faculty of Tanjungpura University for all the supports

AUTHORS CONTRIBUTIONS

Reynaldi MA participated in writing the manuscript, physicochemical properties, and docking analysis, Riza H participated in data interpretations, Luliana S participated in the review of research proposed.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Thomson K, Al-Amin ZM, Al-Qattan KK, Shaban LH, Ali M. Anti-diabetic and hypolipidaemic properties of garlic (Allium sativum) in streptozotocin-induced diabetic rats. Int J Diabetic Metabolism 2007;15:108-15.
2. World Health Organization, Global Report on Diabetes; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf. [Last accessed on 28 Nov 2017]
3. Kementerian Kesehatan Republik Indonesia, Situasi dan Analisis Diabetes; 2014. Available from: http://www.depkes.go.id/resources/download/pusdatin/infodatin/infodatin-diabetes.pdf. [Last accessed on 28 Nov 2017]
4. Gilbert B, Alves LF. Synergy in plant medicine. Curr Med Chem 2003;10:13-20.
5. Ojo RJ, Memudu AE, Akintayo CO, Akpan IS. Preventive effect of allium sativum on alloxan induced diabetic rat. ARPN J Agric Bio Sci 2012;7:609-12.

6. Block JH. Drug design strategies. In: Beale JM, Block JH. Eds. Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry. 12th Ed. Philadelphia: Lippincott Williams and Wilkins; 2011. p. 38-9.
7. Jensen F. Introduction to computational chemistry. 2nd Ed. Hoboken: United States: John Wiley and Sons Ltd; 2006. p. 69-416.
8. Krovat EM, Steindl T, Langer T. Recent advances in docking and scoring. Curr Computer-Aided Drug Design 2005;1:93-102.
9. Kapetanovic IM. Computer-aided drug discovery and development: *in silico*-chemico-biological approach. Chem Biol Interact 2008;171:165–76.
10. Saini V. Moleculer mechanism of insulin resistance in type 2 diabetic mellitus. World J Diabetic 2010;1:68-75.
11. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest 2013;123:2764-72.
12. Coman C, Socaciu C. Docking of phytochemicals to the peroxisome proliferator-activated receptor gamma. Bull UASVM Agric 2012;69:236-42.
13. ChemOffice protocol; 2017. Available from: http://www.cambridgesoft.com/Ensemble_for_Chemistry/details/Default.aspx?fid=16andpid=735. [Last accessed on 20 Jan 2017]
14. Yanuar A. Penambatan molekuler. Praktek dan aplikasi pada virtual screening. Depok: Fakultas Farmasi Universitas Indonesia; 2012. p. 43-93.
15. Zaitseva J, Oswald C, Jumpertz T, Janewein S, Wiedenann A, Holland IB, *et al*. A structural analysis of asymmetry required for catalytic activity of an ABC-ATPase domain dimer. EMBO J 2006;25:3432-43.
16. National Centre for Biotechnology Information; 2016. Available from: https://www.ncbi.nlm.nih.gov/protein/341941160?log$=activity. [Last accessed on 23 Dec 2016]
17. Li Y, Wang Z, Furukawa N, Escaron P, Weiszmann J, Lee G, *et al.* T2384, a novel antidiabetic agent with unique peroxisome proliferator-activated receptor γ binding properties. J Bio Chem 2008;283:9168-76.
18. Chan SL, Labute P. Training a scoring function for the alignment of small molecules. J Chem Inf Model 2010;50:1724–35.
19. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Delivery Rev 2000;46:3-26.
20. Trott O, Olson JA. AutoDockVina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comp Chem 2010;31:455-61.
21. Vaiyapuri S, Shruthi SD. *In vitro* and *in silico* antidiabetic activity of pyran ester derivative isolated from tragia cannabina. Asian Pac J Trop Biomed 2014;4:S454-9.
22. Vineet M, Arun S, Pallavi K, Udayabanu M. Antioxidant, anti-inflammatory, and antidiabetic activity of hydroalcoholic extract of ocimum sanctum: an *in vitro* and *in silico* study. Asian J Pharm Clin Res 2016;9:44-9.
23. Jensen F. Introduction to computational chemistry. 2nd Ed. Denmark: John Wiley and Sons, Ltd; 2007. p. 1-21.